

## Answering reviewers

Dear editor,

Thank you very much for giving us an opportunity to revise our manuscript. We appreciate the editor and reviewers very much for their constructive comments and suggestions on our manuscript entitled "Mesenterico-portal vein invasion should be an important factor in TNM staging for pancreatic ductal adenocarcinoma: proposed modification of the 8th edition of the AJCC staging system" (Manuscript No: 51570).

We have studied reviewers' comments carefully. According to the reviewers' detailed suggestions, we have made a careful revision on the original manuscript. All revised portions are marked in red in the revised manuscript which we would like to submit for your kind consideration.

Kind regards.

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Dear reviewers:

Thank you for your comments on our manuscript entitled "Mesenterico-portal vein invasion should be an important factor in TNM staging for pancreatic ductal adenocarcinoma: proposed modification of the 8th edition of the AJCC staging system" (Manuscript No: 51570). Those comments are very helpful for revising and improving our paper. We have studied the comments carefully and made corrections which we hope meet with approval. The main corrections are in the manuscript and below we present a point-by-point response to reviewers' comments. (the replies are highlighted in blue).

Replies to the reviewers' comments:

reviewer #1

1. Did the conditions of Cox regression be evaluated? If not, please evaluate the assumption of Cox by testing strategies (PMID 20233435)

Response: We followed the suggestion and verified the proportional hazard assumption. The time-varying effect of numeric variable (age) was verified by Schoenfeld residual method, and the time-varying effect of nominal data were showed with the log of minus the log of the survival functions. We decided to remove the variable age from the Cox regression since it has time-varying effect in the SEER database.

2. Did MPV(+) patients with CA, SMA and/or CHA metastasis?

Response: As described in the section *methods*, only patients with stage T1~3N0~2M0

tumors were included from the West China Hospital database. Tumors with CA, SMA and/or CHA invasion were staged as T4, so these patients were not with CA, SMA and /or CHA invasion. However, in the SEER database, only the data which contribute to the 7th edition of the AJCC staging were recorded, that is, SMA and/or CA invasion. Therefore, it's unable to exclude patients with CHA invasion.

3. Did CA, SMA and/or CHA influent the survival of patients?

Response: Since we only included patients with stage T1~3N0~2M0 tumors, the patients from the SEER database did not have CA/SMA invaded by the tumors, and the patients from the West China Hospital database did not have CA/SMA/CHA invaded. There might be patients with CHA invasion in the MPV(+) group of the SEER cohort. Although CHA invasion were believed to influent the survival of patients that patients with CHA were reclassified as T4 tumors in the 8th edition of AJCC staging, the proportion of these patients is limited. We report in the West China Hospital database (not the population that we studied, it's the entire database) the proportion of patients with tumor that invaded CHA and did not invaded CA/SMA was 0.00%.

4. The Harrell concordance index is the method which can compared the performace of two stage. Thus, please perform this assay with SEER cohort and West China cohort

Response: We thank the reviewer and follow this suggestion. Since the work covered both the T staging and the TNM staging, we still calculate the Harrell C-index for the T staging and for the TNM staging. Of the entire population included in this study, the C-index for the 8th edition of the AJCC staging system was 0.572 in SEER database and 0.602 in West China Hospital database, and the modified staging system was 0.578 in SEER database and 0.620 in West China Hospital database. In patients with N0 diseases, The C-index for the T staging of the 8th edition was 0.552 in the SEER database and 0.578 in West China Hospital database, and those for the modified T staging was 0.556 in SEER database and 0.584 in West China Hospital database.

reviewer #2

(1) In the abstract, what is two cohorts? No concrete database is mentioned Actually, SEER database and the West China Hospital database are used.

Response: The first cohort used the data from SEER database, and the second cohort enrolled the patients from the West China Hospital database. We did not combine the data from the two databases for analysis.

(2) In SEER database, does MPV+ mean microscopic invasion of PV?

Response: MPV+ group in the SEER database, or rather, the extension-540 group represents the patients with tumor invading gastroduodenal artery, hepatic artery, pancreaticoduodenal artery, portal vein, superior mesenteric vein or transverse colon which did not invade the SMA, CA, Aorta or distant organs (otherwise another code is used). In the section *limitations* we have discussed: although few patients in West China Hospital database had GDA, hepatic artery, PDA or transverse colon invasions, these does exist in the SEER database and may affect the results of the survival analysis. Therefore, the SEER database had a large sample

size, but there may be biases in the results; West China Hospital database ensured that patients in the MPV+ group have microscopic invasion of MPV, but the sample size is small. In the patients with T1~T3 tumors, the extension variables of individuals with MPV invasion were recorded as 540; and in patients with T4 tumors, it is not possible to determine whether the tumor invaded MPV: this is also one of the reasons that we did not include T4 tumor into analysis.

(3) In West China Hospital database, did you include the patients who had invasion of SMA and CA? There is no description about this.

Response: Patients in the West China Hospital database were not with SMA and CA invasion. Tumors with SMA and CA invasion were staged as T4. As described in the section *methods*, only patients with stage T1~3N0~2M0 tumors were included.

(4) The rate of postindustrial (positive?) lymph node metastatic seems to be significantly higher in SEER database compared to West China Hospital database: about 70 % vs. about 50%, as shown in Table. The authors should mention it.

Response: We have noticed this difference when processing data, but there is no way to explain this difference in retrospective studies.

(5) In Table 3, what does the number in parentheses mean?

Response: The number in the parentheses are standard error of median survival and standard error of survival rate.

(6) Did you assess the impact of other extrapancreatic tissue invasion on the prognosis of patients ?

Response: When we conceived the idea for this study, we compared the survival of patients with several different types of extrapancreatic tissue invasions (including the common bile duct and gallbladder invasion, duodenum invasion, and portal vein invasion and other extrapancreatic tissue invasion) in our data with those without extrapancreatic tissue invasion. Then, we found that only patients with portal vein invasion has significant shorter survival than the patients without extrapancreatic tissue invasion, so we chose portal vein invasion as the topic of this article.

(7) You excluded the patients who had 5 or fewer lymph nodes examined. Why did you use "five" for the cutoff line?

Response: According to the consensus reached at the ISGPS conference, the number of lymph nodes examined in pancreatic cancer surgical specimens should be 15 or more. Removing patients with number of lymph nodes examined below 15 will delete the 40~50% of the population, and the remaining patients do not represent the actual survival rate of the entire population; if not removed, the patients who should be classified as with N1, N2 diseases were staged as with N0 diseases leading to bias. We chose a compromise and deleted patients with the number lymph node examined 5 or less (N=836 in the SEER database and N=69 in West China Hospital database). The remaining population (about 90% in size) can be divided into 3 groups with the N classification and can well represent the survival of the actual

patient population.

(8) I could not open the HP of CS even if using the URL you described in the reference 3. What is the specific contents of the “patients with tumors with CS extension data labeled “540””? Would you give me the reference as a PDF file ?

Response: [We attached the pdf printed on the webpage.](#)

Once again, thank you very much for your constructive comments and suggestions which would help us both in English and in depth to improve the quality of the paper.

Kind regards,

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